JERUSSI CONSULTING, INC.

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August 11, 2003

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

SUITABILITY PETITION

Dear Sir/Madam:

Jerussi Consulting, Inc. submits this petition pursuant to 21 C.F.R. " 10.25(a) and 10.30 and in accordance with the regulations at 21 C.F.R. ' 314.122 to request that the Commissioner of the Food and Drug Administration ("Commissioner") make a determination that a topical solution for the drug product NDA #20-922, Solagè for the treatment of Lentigo, solar. will be an acceptable substitution of one active ingredient (Mequinol) for an equivalent, hydroquinone. Attachment I contains literature references demonstrating the equivalence of the pharmacodynamics for hydoquinone compared to 4-hydroxy-anisole (4-methyl ether of hydroquinone}. Further support of the pharmacological equivalence of hydroquinone to mequinol is found in a number of prescription and over the counter formulae containing hydroquinone for the de-pigmentation of skin by topical application. A review of the summary basis for approval for NDA: 20-922, Solagè, shows the comment from the agency as, "4-hydroxyanisole is the monomethyl ether of hydroquinone". Hydroquinone is a proven skin bleaching agent, marketed in United States in OTC preparations at concentrations of 1.5% and 2% and in prescription products in 3% and 4%. 4-hydroxyanisole has been marketed in Europe and other countries at concentrations of 5-20% and has also been used as an antioxidant in cosmetic products in the US at concentrations up to 1%". Having said this, it is already recognized that the equivalence of these two drug substances exists by the FDA.

A. Action Requested

The petitioner requests that the Commissioner make a determination that the Galderma product, Solagè containing 2% Mequinol, and 0.01% tretinoin, NDA #20-922 can be formulated as a topical solution with the substitution of Hydroquinone at 4% for the 2% Mequinol and filed as an abbreviated New Drug Application referencing Solagè, NDA 20-922 as the Reference Listed Drug (RLD).

B. Statement of Grounds

The Orange Book lists the approval of Solagè, Active Ingredients; Mequinol and Tretinoin, at strengths 2% and 0.01% respectively as NDA #20-922 to the applicant Galderma. The dosage

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form approved and route of administration is a topical solution. Jerussi Consulting, Inc. plans to develop the alternate formula containing hydroquinone and tretinoin at the prescribed strength , applicability, and stability. Further, the Waxman/Hatch 1984 law, permits the substitution of a equivalent active ingredients 314.161(a)(1), FDA must make a determination as to whether a listed drug is substitutable for reasons of safety or effectiveness before an ANDA using that listed drug as an RLD may be approved.

Solagè Topical Solution currently listed in the Orange Book 021112, TE code (none listed) is an alcoholic based topically applied solution. The summary basis of approval NDA 20-922 suggests the chemistry, manufacturing and controls required no additional studies. The active pharmaceutical ingredients contained, are referenced to other product containing the active ingredients in topical administrated dosages such as creams and topical solutions, e.g.,

Hydroquinone	Tretinoin
Tri-Luma, 21112, Hilldermic	20438, Roche (oral)
4% hydroquinone Cream, ICN; Medicus	19049, 17522, 17340 Johnson & Johnson (cream)
4% hydroquinone Gel, ICN	17955, 17579, Johnson & Johnson (Gel)
Solution, Neutrogena	16921, Johnson & Johnson (Solution)
Hydroquinone w/ sunscreen (Ethex)	20475, Johnson & Johnson (Φ-sphere gel)
Eldopaque Forte (ICN	19963, Johnson & Johnson (emollient cream)
Glyquin (ICN)	20886, Ligand (gel)
Solaquin (ICN)	20400 Bertek (gel)
Alustra Cream (Medicis)	20404 Bertek (gel)
Lustra Cream (Medicis)	20922, Galderma (Solution)
	75264, 75265, 75213 Spear Pharm (Cream)
	75589, 75529 Spear Pharm (Gel)
	74873, Copley (Solution)
	75260, Morton Grove (Solution)
	21112, Hill (Cream)

The above tabled products are all prescription strength of hydroquinone, at 4% w/w.

C. Environmental Impact

An environmental assessment on the action requested in this petition qualifies for a categorical exclusion under 21 C.F.R. ' 25.31. Therefore, an environmental assessment is not required for the requested action.

D. Economic Impact

Pursuant to 21 C.F.R. ' 10.30(b), economic impact information is to be submitted only when requested by the Commissioner. Jerussi will promptly provide such information if so requested.

E. Certification

Jerussi certifies that, to the best of its knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Robert A. Jerussi

Robert A. Jerussi, Ph.D.
Jerussi Consulting, Inc.

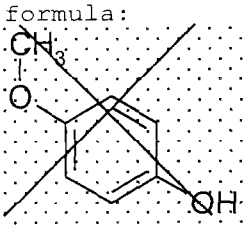
Rx only

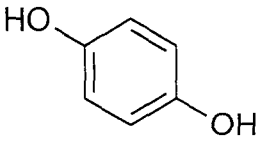
~~Solagé™~~
(~~mequinol 2%~~ **Hydroquinone 4%**, tretinoin 0.01%)
Topical Solution
For Dermatologic use only. Not for ophthalmic, oral or intravaginal use.

DESCRIPTION

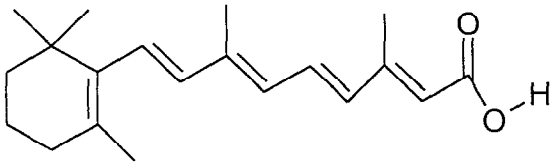
~~Solagé™~~ Topical Solution contains ~~mequinol 2%~~ **Hydroquinone 4%** and tretinoin 0.01%, by weight, in a solution base of ethyl alcohol (77.8% v/v), polyethylene glycol ~~400~~,**800** butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, and **tocopherol** disodium and purified water.

Hydroquinone is p-di-hydroxybenzene. ~~4- hydroxyanisole, the monomethyl ether of hydroquinone or 1-hydroxy-4-methoxybenzene.~~ It has the chemical formula, C**6**H**6**O2, a molecular weight of ~~124.14~~ **110.11**, and the structural formula:





The chemical name for tretinoin, a retinoid, is (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid, also referred to as all-trans-retinoic acid. It has the chemical formula, C20H28O2, a molecular weight of 300.44, and the structural formula:



CLINICAL PHARMACOLOGY

Solar lentigines are localized, pigmented, macular lesions of the skin on the areas of the body which have been chronically exposed to sunlight. ~~Biopsy specimens of solar lentigines were collected in a clinical study with Solagé Solution at baseline, at the end of a 24 week treatment period and at the end of a subsequent 24 week, no treatment, follow-up period. The end of treatment specimens showed a decrease in melanin pigmentation in both melanocytes and keratinocytes, and an increased lymphocytic infiltration, which may have been the result of irritation or an immunologic reaction. The end of follow-up period specimens showed repigmentation of the melanocytes and keratinocytes to a state similar to the baseline specimens. These results indicate that there is no assurance that any improvement obtained would persist upon discontinuation of drug therapy.~~

The mechanism of action of ~~mequinol~~ **Hydroquinone** is unknown. Although ~~mequinol~~ **Hydroquinone** is a substrate for the enzyme tyrosinase and acts as a competitive inhibitor of the formation of melanin precursors, the clinical significance of these findings is unknown. The mechanism of action of tretinoin as a depigmenting agent also is unknown.

PHARMACOKINETICS

~~The percutaneous absorption of tretinoin and the systemic exposure to tretinoin and mequinol~~ **Hydroquinone** ~~were assessed in healthy subjects (n=8) following two weeks of twice daily topical treatment of Solagé Solution. Approximately 0.8 mL of Solagé Solution was applied to a 400 cm2 area of the back, corresponding to a dose of 37.3 µg/cm2 for mequinol and 0.23 µg/cm2 for tretinoin. The percutaneous absorption of tretinoin was approximately 4.4%, and systemic concentrations did not increase over endogenous levels. The mean Cmax for mequinol~~ **Hydroquinone** ~~was 9.92 ng/mL (range 4.22 to 23.62 ng/mL) and the Tmax was 2 hours (range 1 to 2 hours).~~

INDICATIONS AND USAGE

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling).

~~Solagé~~ (~~mequinol 2%~~ **Hydroquinone** 4%, tretinoin 0.01%) Topical Solution is indicated for the treatment of solar lentigines.

~~Solagé~~ **The Topical Solution** should only be used under medical supervision as an adjunct to a comprehensive skin care and sun avoidance program where the patient should primarily either avoid the sun or use protective clothing.

Neither the safety nor effectiveness of ~~Solagé~~ **The Topical Solution** for the prevention or treatment of melasma or postinflammatory hyperpigmentation has been established.

The efficacy of using ~~Solagé~~ **The Topical Solution** daily for greater than 24 weeks has not been established.

The local cutaneous safety of using ~~Solagé~~ **The Topical Solution** in non-Caucasians has not been adequately established (see **Clinical Studies section**).

CONTRAINDICATIONS

The combination of ~~mequinol~~ **Hydroquinone** and tretinoin may cause fetal harm when administered to a pregnant woman. Due to the known effects of these active ingredients, ~~Solagé~~ Topical Solution should not be used in women of childbearing potential. In a dermal teratology study in New Zealand White rabbits, there were no statistically significant differences among treatment groups in fetal malformation data; however, marked hydrocephaly with visible doming of the head was observed in one mid-dose litter (12 and 0.06 mg/kg or 132 and 0.66 mg/m2 of mequinol and tretinoin, respectively) and two fetuses in one high dose litter (40 and 0.2 mg/kg or 440 and 2.2 mg/m2 of mequinol and tretinoin, respectively) of ~~Solagé~~ Solution, and two high-dose tretinoin (0.2 mg/kg, 2.2 mg/m2) treated litters. These malformations were considered to be treatment related and due to the known effects of tretinoin. This was further supported by coincident appearance of other malformations associated with tretinoin, such as cleft palate and appendicular skeletal defects. No effects attributed to treatment were observed in rabbits in that study treated topically with mequinol ~~Hydroquinone~~ alone (dose 40 mg/kg, 440 mg/m2). A no-observed-effect level (NOEL) for teratogenicity in rabbits was established at 4 and 0.02 mg/kg (44 and 0.22 mg/m2 mequinol ~~Hydroquinone~~ and tretinoin, respectively) for ~~Solagé~~ Solution which is approximately the maximum possible human daily dose, based on clinical application to 5% of total body surface area. Plasma tretinoin concentrations were not raised above endogenous levels, even at teratogenic doses. Plasma ~~mequinol~~ **Hydroquinone** concentrations in

rabbits at the NOEL at one hour after application were 124 ng/mL or approximately twelve times the mean peak plasma concentrations of that substance seen in human subjects in a clinical pharmacokinetic study. In a repeated study in pregnant rabbits administered the same dose levels as the study described above, additional precautionary measures were taken to prevent ingestion, although there is no evidence to confirm that ingestion occurred in the initial study. Precautionary measures additionally limited transdermal absorption to a six hour exposure period, or approximately one-fourth of the human clinical daily continuous exposure time. This study did not show any significant teratogenic effects at doses up to approximately 13 times the human dose on a mg/m2 basis. However, a concurrent tretinoin dose group (0.2 mg/kg/day) did include two litters with limb malformations. ~~In a published study in albino rats (J. Am. Coll. Toxicology 4(5):31-63, 1985), topical application of 5% of mequinol~~ **Hydroquinone** ~~in a cream vehicle during gestation was embryotoxic and embryolethal. Embryonic loss prior to implantation was noted in that study where animals were treated throughout gestation. Coincidentally, mean preimplantation embryonic loss was increased in the first rabbit study in all mequinol~~ **Hydroquinone** ~~treated groups, relative to control, and in the high dose mequinol~~ **Hydroquinone** ~~/tretinoin and tretinoin only treated groups in the second study. In those studies, dosing began at gestation day 6, when implantation is purported to occur. Increased preimplantation loss was also noted at the high combination dose in a study of early embryonic effects in rats, as was decreased body weight in male pups; these findings are consistent with the published study.~~

~~Solagé~~ Solution was not teratogenic in Sprague-Dawley rats when given in topical doses of 80 and 0.4 mg/kg mequinol ~~**Hydroquinone**~~ and tretinoin, respectively (480 and 2.4 mg/m2 or 11 times the maximum human daily dose). The maximum human dose is defined as the amount of solution applied daily to 5% of the total body surface area. With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no casual association has been established from these cases, 6 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known. No adequate or well-controlled trials have been conducted with ~~Solagé~~ Solution in pregnant women. ~~Solagé~~ Topical Solution is contraindicated in individuals with a history of sensitivity reactions to any of its ingredients. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS

~~Solagé~~ **The Topical Solution** is a dermal irritant and the results of continued irritation of the skin for greater than 52 weeks in chronic, long-term use are not known. Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with utmost caution in patients with this condition. Safety and effectiveness of ~~Solagé~~ Solution in individuals with moderately or heavily pigmented skin have not been established.

~~Solagé~~ Solution should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity. Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) to treated areas should be avoided or minimized during the use of ~~Solagé~~ **The Topical Solution**. Patients must be advised to use protective clothing and comply with a comprehensive sun avoidance program when using ~~Solagé~~ Solution. Data are not available to establish how or

whether ~~Solagé~~ Solution is degraded (either by sunlight or by normal interior lighting) following application to the skin. Patients with sunburn should be advised not to use ~~Solagé~~ Solution until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using ~~Solagé~~ Solution and ensure that the precautions outlined in the Patient Medication Guide are observed. ~~Solagé~~ Solution should be kept out of the eyes, mouth, paranasal creases, and mucous membranes. ~~Solagé~~ Solution may cause skin irritation, erythema, burning, stinging or tingling, peeling, and pruritis. If the degree of such local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether. The efficacy at reduced frequencies of application has not been established. ~~Solagé~~ **The Topical Solution** should be used with caution by patients with a history, or family history, of vitiligo. One patient in the trials, whose brother had vitiligo, experienced hypopigmentation in areas that had not been treated with study medication. Some of these areas continued to worsen for at least one month post treatment with ~~Solagé~~ Solution. Six weeks later the severity of the hypopigmentation had decreased from moderate to mild and 106 days post treatment, the patient had resolution of some but not all lesions. Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, discomfort, or hypopigmentation of the skin may occur.

PRECAUTIONS

General

For external use only.

~~Solagé~~ **The Topical Solution** should only be used as an adjunct to a comprehensive skin care and sun avoidance program. (See INDICATIONS AND USAGE section).

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of ~~Solagé~~ **The Topical Solution** should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using ~~Solagé~~ Solution.

Information for patients

Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety. The Patient Medication Guide is attached to this Package Insert.

Drug Interactions Concomitant topical products with a strong skin drying effect, products with high concentrations of alcohol, astringents, spices or lime, medicated soaps or shampoos, permanent wave solutions, electrolysis, hair depilatories or waxes, or other preparations that might dry or irritate the skin should be used with caution in patients being treated with ~~Solagé~~ **The Topical Solution** because they may increase irritation when used with ~~Solagé~~ Solution. ~~Solagé~~ Solution should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility

~~Although a dermal carcinogenicity study in CD-1 mice indicated that Solagé Solution applied topically at daily doses up to 80 and 0.4 mg/kg (240 and 1.2 mg/m2) of mequinol **Hydroquinone** and tretinoin, respectively, representing approximately 5 times the maximum possible systemic human exposure was not carcinogenic, in a photocarcinogenicity study utilizing Crl:Skh-1(hr/hr BR) hairless albino mice, median time to onset of tumors decreased. Also, the number of tumors increased in all dose groups administered 1.4, 4.3 or 14 µl of Solagé Solution/cm2 of skin (24 and 0.12, 72 and 0.36, or 240 and 1.2~~

~~mg/m2 of mequinol~~ **Hydroquinone** ~~and tretinoin, respectively; 0.6, 1.9, or 6.5 times the daily human dose on a mg/m2 basis) following chronic topical dosing with intercurrent exposure to ultraviolet radiation for up to 40 weeks. Similar animal studies have shown an increased tumorigenic risk with the use of retinoids when followed by ultraviolet radiation. Although the significance of these studies to human use is not clear, patients using this product should be advised to avoid or minimize exposure to either sunlight or artificial ultraviolet irradiation sources.~~

~~Solagé~~™ Topical Solution Medication Guide
(~~mequinol~~ **Hydroquinone** 4%, tretinoin 0.01%)
Hydroquinone was non-mutagenic in the Ames/Salmonella assay using strains TA98, TA100, TA1535, and TA1537, all of which are insensitive to mutagenic effects of structurally-related quinones. ~~Solagé~~ **The Topical Solution** was non-genotoxic in an in vivo dermal micronucleus assay in rats, but exposure of bone marrow to drug was not demonstrated. A dermal reproduction study with ~~Solagé~~ Solution in Sprague-Dawley rats at a daily dose of 80 and 0.4 mg/kg (480 and 2.4 mg/m2) of ~~mequinol~~ **Hydroquinone** and tretinoin, respectively, approximately 11 times the corresponding maximum possible human exposure, assuming 100% bioavailability following topical application to 5% of the total body surface area, showed no impairment of fertility.
Pregnancy: Teratogenic effects: Pregnancy Category X.
Although the magnitude of the potential for teratogenicity may not be well-defined, ~~Solagé~~ **The Topical Solution** is labeled as an "X" because the potential risk of the use of this drug to treat this particular indication (solar lentigines) in a pregnant woman clearly outweighs any possible benefit (see CONTRAINDICATIONS section).Nursing Mothers: It is not known to what extent ~~mequinol~~ **Hydroquinone** and/or tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ~~Solagé~~ **The Topical Solution** is administered to a nursing woman.
Pediatric Use: The safety and effectiveness of this product have not been established in pediatric patients. ~~Solagé~~ **The Topical Solution** should not be used on children.
Geriatric Use: Of the total number of patients in clinical studies of ~~Solagé~~ **The Topical Solution**, approximately 43% were 65 and older, while approximately 8% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients.
ADVERSE REACTIONS
In clinical trials, adverse reactions were primarily mild to moderate in intensity, occurring in 66% and 30% of patients, respectively. The majority of these events were limited to the skin and 64% had an onset of a skin related adverse reaction early in treatment (by week 8). The most frequent adverse reactions in patients treated with ~~Solagé~~ **The Topical Solution** were erythema (49% of patients), burning, stinging, or tingling (26%), desquamation (14%), pruritus (12%), and skin irritation (5%). Some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%). Ninety-four of 106 patients (89%) had resolution of hypopigmentation upon discontinuation of treatment to the lesion, and/or re-instruction on proper application to the lesion only. Another 8% (9/106) of patients with hypopigmentation events had resolution within 120 days after the end of treatment. Three of the 106 patients (2.8%) had persistence of hypopigmentation beyond 120 days. Approximately 6% of patients discontinued study participation with ~~Solagé~~ **The Topical Solution** due to adverse reactions. These discontinuations were due primarily to skin redness (erythema) or related cutaneous adverse reactions. ~~Solagé~~ Solution was generally well tolerated.
Adverse Events Occurring in >1% of the Population –All Studies

~~Body System Solagé Solution~~

~~(mequinol **Hydroquinone** 4%,~~
~~tretinoin 0.01%)~~
~~44.6 549~~
~~N % N % N % N %~~
~~4.6~~
~~11.4 21.9 270~~
~~12.6 155~~
~~11.0~~
~~Skin and Appendages~~ ~~76~~
~~Erythema~~ ~~50~~
~~Burning/Stinging/~~ ~~38~~
~~Tingling~~ ~~31~~
~~Desquamation~~ ~~30~~
~~Pruritus~~ ~~18~~
~~Irritation Skin~~ ~~25~~
~~Halo Hypopigmentation~~ ~~7.3~~
~~Hypopigmentation~~ ~~6.2~~
~~Skin Dry~~ ~~4.1~~
~~Rash~~ ~~3.1~~
~~Crusting~~ ~~2.5~~
~~Rash Vesicular Bullae~~ ~~2.4~~
~~Dermatitis~~ ~~2.1~~
~~135~~ ~~2.0~~
~~90~~

Adverse Events Occurring in >1% of the Population—All Studies								
Body System	Solagé Solution (mequinol 2%, tretinoin 0.01%)		Tretinoin, 0.01%		Mequinol, 2%		Vehicle	
Skin and Appendages	N	%	N	%	N	%	N	%
Erythema	59	44.0	26	55.3	19	6.7	9	4.6
Burning/Stinging/ Tingling	27	21.9	17	36.7	26	10.2	20	11.4
Desquamation	16	12.6	9	19.7	7	2.8	2	1.1
Pruritus	12	11.0	6	14.0	12	4.7	3	1.7
Irritation Skin	9	7.3	3	6.3	1	0.4	1	0.6
Halo Hypopigmentation	7	6.2	1	3.4	2	0.8	2	1.1
Hypopigmentation	5	4.1	1	1.7	2	0.8	0	0.0
Skin Dry	3	3.1	1	3.4	3	1.2	1	0.6
Rash	3	2.5	2	4.4	0	0.0	1	0.6
Crusting	3	2.4	1	3.4	0	0.0	1	0.6
Rash Vesicular Bullae	2	2.1	1	1.7	0	0.0	0	0.0
Dermatitis	2	2.0	0	0.0	0	0.0	0	0.0

OVERDOSAGE

If ~~Solagé~~ **The Topical Solution** is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, discomfort, or

hypopigmentation may occur. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake cf vitamin A (hypervitaminosis A). If oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary. The maximal no-effect level for oral administration of ~~Solagé~~ **The Topical Solution** in rats was 5.0 mL/kg (30 mg/m2). Clinical signs observed were attributed to the high alcohol content (77%) of the drug formulation.

DOSAGE AND ADMINISTRATION

Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety. The physician should review the Patient Medication Guide. Apply ~~Solagé~~ **The Topical Solution** to the solar lentigines using the applicator tip while avoiding application to the surrounding skin. Use twice daily, morning and evening at least 8 hours apart, or as directed by a physician. Patients should not shower or bathe the treatment areas for at least 6 hours after application of ~~Solagé~~ **The Topical Solution.** Special caution should be taken when applying ~~Solagé~~ **The Topical Solution** to avoid the eyes, mouth, paranasal creases, and mucous membranes. Application of ~~Solagé~~ **The Topical Solution** may cause transitory stinging, burning or irritation. Improvement continues gradually through the course of therapy and should be apparent by 24 weeks. Patients should avoid exposure to sunlight (including sunlamps) or wear protective clothing while using ~~Solagé~~ **The Topical Solution.** Data are not available to establish how or whether ~~Solagé~~ Solution is degraded (either by sunlight or by normal interior lighting) Vehicle Hydroquinone,4% Tretinoin, 0.01%

~~8 5.1 55.3 261 13~~
~~20 10.2 36.7 173 26~~
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following application to the skin. With discontinuation of ~~Solagé~~ **The Topical Solution** therapy, a majority of patients will experience some repigmentation over time of their lesions. Applications of larger amounts of medication or more frequently than recommended will not lead to more rapid or better results, and marked redness, peeling, irritation, or hypopigmentation (abnormal lightening) of the skin may occur. Patients treated with ~~Solagé~~ **The Topical Solution** may use cosmetics but should wait 30 minutes before applying. Clinical Studies
Two adequate and well-controlled trials evaluated changes in treated hyperpigmented lesions on the face, forearms/back of hands in 421 patients treated with ~~Solagé~~ Topical Solution, 422 patients treated with tretinoin topical solution, 209 patients treated with ~~mequinol~~ **Hydroquinone** topical solution and 107 patients treated with vehicle for up to 24 weeks. In these studies, patients were to avoid sun exposure and use protective clothing, and use of suncreens was prohibited. Patients were allowed to apply Moisturel® Lotion 30 minutes after application of ~~Solagé~~ **The Topical Solution.** Physicians assessed the extent of improvement or worsening of all the treated lesions from the baseline condition on a 7 point scale. The results of these evaluations are shown below. Forearms/Back of Hands Face Vehicle ~~Solagé~~ **The Topical Solution** Vehicle ~~Solagé~~ Solution 14% 54% 15% 57% Moderate Improvement or greater1 33% 26% 36% 28% Slight Improvement 53% 20% 49% 15% No Change2 12
Includes the following grades: Moderate Improvement, Marked Improvement, Almost Clear, Completely Clear. Moderate Improvement or greater was considered clinically meaningful. Includes the following grades: No Change, Worse (less than 1% of patients treated with ~~Solagé~~ **The Topical Solution** were rated as worse). Improvement (lightening) of the solar lentigines occurred gradually over time during the 24 week treatment period. At 24 weeks of treatment, 57% and 54% of patients experienced moderate improvement or greater, and 3% and 1% of

patients were completely clear of all treated lesions for the face and forearms/back of hands, respectively. It should be noted that approximately 9% of patients, from both treatment areas in these studies, with moderate improvement or greater also experienced hypopigmentation of the skin surrounding at least one treated lesion. There are no vehicle-controlled effectiveness data on the course of lesions treated beyond 24 weeks.
After 24 weeks of treatment, for the forearm/back of hands treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 38%, 37%, and 26%, respectively, and for ~~mequinol~~ **Hydroquinone** topical solution were 24%, 40%, and 36%, respectively. For the face treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 46%, 33%, and 21%, repectively, and for ~~mequinol~~ **Hydroquinone** topical solution were 33%, 30%, and 37% respectively.
The duration of effect was investigated during a period of up to 24 weeks following the discontinuation of treatment. Results from these studies showed that patients may maintain the level of clinical improvement of their treated lesions from the end of treatment through the 24 week follow-up period. However, some degree of repigmentation of treated lesions was observed over time, demonstrating reversibility of the depigmenting action of ~~Solagé~~ **The Topical Solution.**

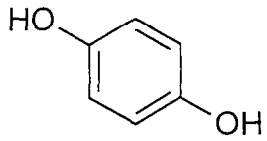
In the clinical studies, some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%). Hypopigmentation of the skin surrounding treated lesions occurs even in the setting of proper application of the drug within the lesion border. The majority (94/106 - 89%) resolved upon discontinuation of treatment to the lesion, and/or re-instruction on proper application to the lesion only. Another 8% (9/106) of patients
with hypopigmentation events had resolution within 120 days after the end of treatment. Three of the 106 patients (2.8%) had persistence of hypopigmentation beyond 120 days. This further demonstrates the reversibility of the depigmenting action of ~~Solagé~~ **The Topical Solution.** Over 150 patients used ~~Solagé~~ Solution twice daily for 52 weeks in an open label clinical study. The safety profile for ~~Solagé~~ Solution in this long-term study was similar to that seen in the 24 week studies although burning/stinging/tingling, desquamation, pruritis, and irritation of the skin occurred at lower rates and halo hypopigmentation and hypopigmentation occurred at a slightly greater rate. Over 90 patients used ~~Solagé~~ Solution twice daily and a concomitant sunscreen (PreSun® 29) daily for up to 24 weeks in an open label clinical study. The safety profile for ~~Solagé~~ **The Topical Solution** in this study was similar to that seen in studies which prohibited sunscreen use although desquamation, pruritis, and halo hypopigmentation occurred at slightly lower rates. The clinical studies of ~~Solagé~~ **The Topical Solution** included 1794 individuals of Skin Type I-V, 94.5% of whom were Caucasian. The trials also included 5% of individuals who were Asian/Pacific Islander- 1.2%, African-American-0.8%, and Hispanic/Latino-3.5%. Safety in Asian/Pacific Islander, African-American, and Hispanic/Latino individuals has not been adequately established. Safety and effectiveness of ~~Solagé~~ Solution in individuals with Skin Type VI (never burns from the sun, deeply pigmented skin) or women of childbearing potential have not been established (see CONTRAINDICATIONS).
HOW SUPPLIED: ~~Solagé~~ (~~mequinol~~ **Hydroquinone** 4%, tretinoin 0.01%) Topical Solution is available in 30 mL plastic bottles with an applicator.

STORAGE: The bottle should be protected from light by continuing to store in the carton after opening. Store at controlled room temperature, 20° - 25° C (68° - 77° F).

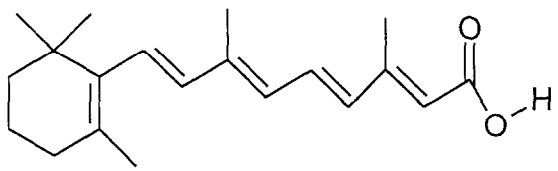
Note: FLAMMABLE. Keep away from heat and open flame.
Marketed by:
~~CALDERMA LABORATORIES, L.P.~~
~~Fort Worth, Texas 76177 USA~~
~~Manufactured by:~~
~~Bristol-Myers Squibb , Buffalo, NY 14213 USA~~
~~P50488-0 Revised August 2002~~

Rx only

Hydroquinone 4%, tretinoin 0.01%)
Topical Solution
For Dermatologic use only. Not for ophthalmic, oral or intravaginal use.
DESCRIPTION
The Topical Solution contains **Hydroquinone 4%** and tretinoin 0.01%, by weight, in a solution base of ethyl alcohol
(77.8% v/v), polyethylene glycol ~~400~~,800 butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, and **tocopherol**
disodium and purified water.
Hydroquinone is p-di-hydroxybenzene It has the chemical
formula, C**6**H**6**O2, a molecular weight of **110.11**, and the structural formula:



The chemical name for tretinoin, a retinoid, is (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic
acid, also referred to as all-trans-retinoic acid. It has the chemical formula, C20H28O2, a molecular weight of
300.44, and the structural formula:



CLINICAL PHARMACOLOGY
Solar lentigines are localized, pigmented, macular lesions of the skin on the areas of the body which have been chronically exposed to sunlight.

The mechanism of action of **Hydroquinone** is unknown. Although **Hydroquinone** is a substrate for the enzyme tyrosinase and acts as a competitive inhibitor of the formation of melanin precursors, the clinical significance of these findings is unknown. The mechanism of action of tretinoin as a depigmenting agent also is unknown.
PHARMACOKINETICS

INDICATIONS AND USAGE
(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling).
(**Hydroquinone** 4%, tretinoin 0.01%) Topical Solution is indicated for the treatment of solar lentigines.
The Topical Solution should only be used under medical supervision as an adjunct to a comprehensive skin care and sun avoidance program where the patient should primarily either avoid the sun or use protective clothing.

Neither the safety nor effectiveness of **The Topical Solution** for the prevention or treatment of melasma or postinflammatory hyperpigmentation has been established.
The efficacy of using **The Topical Solution** daily for greater than 24 weeks has not been established.
The local cutaneous safety of using **The Topical Solution** in non-Caucasians has not been adequately established (see **Clinical Studies section**).

CONTRAINDICATIONS
The combination of **Hydroquinone** and tretinoin may cause fetal harm when administered to a pregnant woman. Due to the known effects of these active ingredients, Topical Solution should not be used in women of childbearing potential. In a dermal teratology study in New Zealand White rabbits, there were no statistically significant differences among treatment groups in fetal malformation data; however, marked hydrocephaly with visible doming of the head was observed in one mid-dose litter (12 and 0.06 mg/kg or 132 and 0.66 mg/m2 of ~~mequinol~~ and tretinoin, respectively) and two fetuses in one high dose litter (40 and 0.2 mg/kg or 440 and 2.2 mg/m2 of mequinol and tretinoin, respectively) of Solution, and two high-dose tretinoin (0.2 mg/kg, 2.2 mg/m2) treated litters. These malformations were considered to be treatment related and due to the known effects of tretinoin. This was further supported by coincident appearance of other malformations associated with tretinoin, such as cleft palate and appendicular skeletal defects. In a repeated study in pregnant rabbits administered the same dose levels as the study described above, additional precautionary measures were taken to prevent ingestion, although there is no evidence to confirm that ingestion occurred in the initial study. Precautionary measures additionally limited transdermal absorption to a six hour exposure period, or approximately one-fourth of the human clinical daily continuous exposure time. This study did not show any significant teratogenic effects at doses up to approximately 13 times the human dose on a mg/m2 basis. However, a concurrent tretinoin dose group (0.2 mg/kg/day) did include two litters with limb malformations. Thirty cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no casual association has been established from these cases, 6 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known. No adequate or well-controlled trials have been conducted with ~~Solagé~~ Solution in pregnant women. The Topical Solution is contraindicated in individuals with a history of sensitivity reactions to any of its ingredients. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS
The Topical Solution is a dermal irritant and the results of continued irritation of the skin for greater than 52 weeks in chronic, long-term use are not known. Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with utmost caution in patients with this condition. Safety and effectiveness of Solution in individuals with moderately or heavily pigmented skin have not been established.
Solution should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity. Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) to treated areas should be avoided or minimized during the use of **The Topical Solution.** Patients must be advised to use protective clothing and comply with a comprehensive sun avoidance program

when using Solution. Data are not available to establish how or whether Solution is degraded (either by sunlight or by normal interior lighting) following application to the skin. Patients with sunburn should be advised not to use Solution until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution
when using Solution and ensure that the precautions outlined in the Patient Medication Guide are observed. Solution should be kept out of the eyes, mouth, paranasal creases, and mucous membranes. Solution
may cause skin irritation, erythema, burning, stinging or tingling, peeling, and pruritis. If the degree of such local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether. The efficacy at reduced frequencies of application has not been established. **The Topical Solution** should be used with caution by patients with a history, or family history, of vitiligo. One patient in the trials, whose brother had vitiligo, experienced hypopigmentation in areas that had not been treated with study medication. Some of these areas continued to worsen for at least one month post treatment with ~~Solagé~~ Solution. Six weeks later the severity of the hypopigmentation had decreased from moderate to mild and 106 days post treatment, the patient had resolution of some but not all lesions.
Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, discomfort, or hypopigmentation of the skin may occur.

PRECAUTIONS

General

For external use only.

~~Solagé~~ **The Topical Solution** should only be used as an adjunct to a comprehensive skin care and sun avoidance program. (See INDICATIONS AND USAGE section).

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of **The Topical Solution** should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using Solution.

Information for patients

Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety. The Patient Medication Guide is attached to this Package Insert.

Drug Interactions Concomitant topical products with a strong skin drying effect, products with high concentrations of alcohol, astringents, spices or lime, medicated soaps or shampoos, permanent wave solutions, electrolysis, hair depilatories or waxes, or other preparations that might dry or irritate the skin should be used with caution in patients being treated with **The Topical Solution** because they may increase irritation when used with Solution.

Solution should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Topical Solution Medication Guide (**Hydroquinone** 4%, tretinoin 0.01%)

Hydroquinone was non-mutagenic in the Ames/Salmonella assay using strains TA98, TA100, TA1535, and TA1537, all of which are insensitive to mutagenic effects of structurally-related quinones. **The Topical Solution** was non-genotoxic in an in vivo dermal micronucleus assay in rats, but exposure of bone marrow to drug was not demonstrated. A dermal reproduction study with ~~Solagé~~ Solution in Sprague-

Dawley rats at a daily dose of 80 and 0.4 mg/kg (480 and 2.4 mg/m2) of **Hydroquinone** and tretinoin, respectively, approximately 11 times the corresponding maximum possible human exposure, assuming 100% bioavailability following topical application to 5% of the total body surface area, showed no impairment of fertility.

Pregnancy: Teratogenic effects: Pregnancy Category X.

Although the magnitude of the potential for teratogenicity may not be well-defined, **The Topical Solution** is labeled as an "X" because the potential risk of the use of this drug to treat this particular indication (solar lentigines) in a pregnant woman clearly outweighs any possible benefit (see CONTRAINDICATIONS section).Nursing Mothers: It is not known to what extent **Hydroquinone** and/or tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **The Topical Solution** is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of this product have not been established in pediatric patients. **The Topical Solution** should not be used on children.

Geriatric Use: Of the total number of patients in clinical studies of **The Topical Solution**, approximately 43% were 65 and older, while approximately 8% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients.

ADVERSE REACTIONS

In clinical trials, adverse reactions were primarily mild to moderate in intensity, occurring in 66% and 30% of patients, respectively. The majority of these events were limited to the skin and 64% had an onset of a skin related adverse reaction early in treatment (by week 8). The most frequent adverse reactions in patients treated with **The Topical Solution** were erythema (49% of patients), burning, stinging, or tingling (26%), desquamation (14%), pruritus (12%), and skin irritation (5%). Some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%). Ninety-four of 106 patients (89%) had resolution of hypopigmentation upon discontinuation of treatment to the lesion, and/or re-instruction on proper application to the lesion only. Another 8% (9/106) of patients with hypopigmentation events had resolution within 120 days after the end of treatment. Three of the 106 patients (2.8%) had persistence of hypopigmentation beyond 120 days. Approximately 6% of patients discontinued study participation with **The Topical Solution** due to adverse reactions. These discontinuations were due primarily to skin redness (erythema) or related cutaneous adverse reactions. ~~Solagé~~ Solution was generally well tolerated.

Adverse Events Occurring in >1% of the Population —All Studies

Solution in this long-term study was similar to that seen in the 24 week studies although burning/stinging/tingling, desquamation, pruritis, and irritation of the skin occurred at lower rates and halo hypopigmentation and hypopigmentation occurred at a slightly greater rate. Over 90 patients used Solution twice daily and a concomitant sunscreen (PreSun® 29) daily for up to 24 weeks in an open label clinical study. The safety profile for **The Topical Solution** in this study was similar to that seen in studies which prohibited sunscreen use although desquamation, pruritis, and halo hypopigmentation occurred at slightly lower rates. The clinical studies of **The Topical Solution** included 1794 individuals of Skin Type I-V, 94.5% of whom were Caucasian. The trials also included 5% of individuals who were Asian/Pacific Islander- 1.2%, African-American-0.8%, and Hispanic/Latino-3.5%. Safety in Asian/Pacific Islander, African-American, and Hispanic/Latino individuals has not been adequately established. Safety and effectiveness of ~~Solagé~~ Solution in individuals with Skin Type VI (never burns from the sun, deeply pigmented skin) or women of childbearing potential have not been established (see CONTRAINDICATIONS).
HOW SUPPLIED: (**Hydroquinone** 4%, tretinoin 0.01%) Topical Solution is available in 30 mL plastic bottles with an applicator.

STORAGE: The bottle should be protected from light by continuing to store in the carton after opening. Store at controlled room temperature, 20° - 25° C (68° - 77° F).
Note: FLAMMABLE. Keep away from heat and open flame.
Marketed by:

INFORMATION FOR PATIENTS

Please read this Medication Guide carefully before you start to use your medicine. If you have any questions, or are not sure about any of the information on ~~Solagé~~ Solution, ask your doctor.

The active ingredients in ~~Solagé~~ Solution (pronounced so-la-JAY) are mequinol and tretinoin.

~~Solagé~~ Solution also contains ethlyl alcohol (77.8% v/v), polyethylene glycol 400, butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, edetate disodium, and purified water.

What is the Most Important Information about ~~Solagé~~ Solution?

~~Solagé~~ Solution is a prescription medication. It should only be used under supervision of your doctor as part of a sun avoidance program. This program should also include avoiding exposure to artificial sunlight (sunlamps) and avoidance of direct sunlight by wearing protective clothing.

~~Solagé~~ Solution does not permanently "cure" solar lentigines, also known as brown "age" or "liver" spots. In clinical trials, most patients experienced some degree of darkening of their spots over time.

Follow the instructions for application of ~~Solagé~~ Solution carefully. Avoid getting the medication on your normal-toned skin, in your eyes, nose, or mouth.

~~Solagé~~ Solution can cause the side effect, halo hypopigmentation, which is lightening of the skin surrounding the spot being treated, within the 6 month treatment period.

Warning: ~~Solagé~~ Solution should not be used if you are pregnant, attempting to become pregnant, or at a high risk of pregnancy. Consult your doctor for adequate birth control measures if you are a female of child-bearing potential.

Avoid sunlight and any other medicines that may increase your sensitivity to sunlight (see below).

There is very limited information on the safety of ~~Solagé~~ Solution in people with moderately or darkly pigmented skin.

What Can I Expect From ~~Solagé~~ Solution?

~~Solagé~~ Solution is a prescription medication used for the topical treatment of solar lentigines, also known as brown "age" or "liver" spots.

Studies show that after 24 weeks, for lesions of the face, 57% of patients using ~~Solagé~~ Solution had moderate improvement or greater, with 3% experiencing complete clearing of all treated lesions. Another 28% of patients had slight improvement and 15% had no change or worse (less than 1% of patients had worsening of their lesions). After 24 weeks for lesions of the forearms/back of hands, 54% of patients using ~~Solagé~~ Solution experienced moderate improvement or greater, with 1% experiencing complete clearing of all treated lesions. Another 26% had slight improvement and 20% had no change or worse (less than 1% of patients had worsening of their lesions).

Approximately 9% of patients who had success in the treatment of their age spots also experienced the side effect, halo hypopigmentation, which is lightening of skin surrounding the treated spot.

Evidence has not been established concerning the effectiveness of ~~Solagé~~ Solution in the treatment of other hyperpigmented conditions of the skin.

Improvement in the color of the treated age spots occurs gradually. Don't be discouraged if you see no immediate

improvement. Be patient. If ~~Solagé~~ Solution is going to have a beneficial effect for you, it may take up to six months of
treatment before full beneficial effects are seen. After stopping treatment with ~~Solagé~~ Solution, the age spots may
darken again over time.
The effectiveness of ~~Solagé~~ Solution in treating solar lentigines, also known as brown "age" or "liver" spots, beyond 6
months has not been established.
Who should not use ~~Solagé~~ Solution?
~~Solagé~~ Solution should not be used if you are pregnant, attempting to become pregnant, or at a high risk of pregnancy.
Consult your doctor for adequate birth control measures if you are a female of child-bearing potential.
It is not known if ~~Solagé~~ Solution is passed to infants through breast milk. Do not use ~~Solagé~~ Solution if you intend to
breast feed, unless advised otherwise by your doctor.
~~Solagé~~ Solutuion should not be used on children.
Do not use ~~Solagé~~ Solution if you are allergic to any ingredients in this medicine. If you are allergic to any of the ingredients,
tell your doctor.
If you are sunburned, do not use ~~Solagé~~ Solution until you have fully recovered.
Do not use ~~Solagé~~ Solution if you have a skin condition called eczema or other inflamed or irritated chronic skin conditions.
Do not use ~~Solagé~~ Solution if you are inherently sensitive to sunlight or taking other drugs that increase your sensitivity
to sunlight. You should tell your physician if you are also using other medicines that increase sensitivity to sunlight.
These medications include but are not limited to: thiazides (used to treat high blood pressure), tetracyclines, fluroquinolones
or sulfonamides (used to treat infection), and phenothiazines (used to treat serious emotional problems). If
you are taking any prescription medicines, non-prescription medicines or using any facial or skin creams, check with
your physician to make sure they do not interact with ~~Solagé~~ Solution.
There is very limited information on the safety of ~~Solagé~~ Solution in people with moderately or darkly pigmented skin.
If you, or a family member, have a history of vitiligo (a skin condition consisting of white patches on various parts of
the body), consult your doctor before using ~~Solagé~~ Solution.
How should I use ~~Solagé~~ Solution?
~~Solagé~~ Solution is to be used twice daily, at least eight hours apart, or as directed by your doctor. It is a drug for topical
use only and is not a cosmetic preparation. Do not use ~~Solagé~~ Solution around your eyes, lips, creases of the nose
or mucous membranes. ~~Solagé~~ Solution may cause severe redness, itching, burning, stinging, and peeling if applied
to these areas. If the product gets in your eyes, rinse thoroughly with water and contact your doctor.
Apply ~~Solagé~~ Solution to the age spots using the applicator provided with the medication. Avoid application of ~~Solagé~~
Solution to the surrounding, normally colored skin. Only enough ~~Solagé~~ Solution should be applied to make the lesion
appear moist - running or dripping of the medication should be avoided.
Applications of larger amounts of ~~Solagé~~
Solution, or more frequent applications than recommended, will not lead to more rapid or better results, and marked

redness, peeling, irritation or hypopigmentation may occur. You should not shower or bathe the treatment areas for at least 6 hours after application of ~~Solagé~~ Solution.

Stop treating any age spots that become the same color or lighter than your normally colored skin. If the skin surrounding an age spot becomes lighter than your normally colored skin, stop treating that age spot and contact your doctor regarding continued use of ~~Solagé~~ Solution to that age spot.

If you forget or miss a dose of ~~Solagé~~ Solution, do not try to "make it up." Return to your normal application schedule as soon as you can.

If sensitivity or increased irritation occurs, stop use of ~~Solagé~~ Solution and contact your doctor.

If the age spots become darker with treatment, stop use of ~~Solagé~~ Solution and contact your doctor.

Do not use ~~Solagé~~ Solution for any condition other than for which it was prescribed by your doctor. Do not give it to other persons or allow other persons to use it.

You may use cosmetics after applying ~~Solagé~~ Solution but you should wait 30 minutes before applying.

What should I avoid while using ~~Solagé~~ Solution?

~~Solagé~~ Solution increases your sensitivity to sunlight. Sun exposure (natural or artificial) to areas of the skin treated with ~~Solagé~~ Solution should be avoided. Wear protective clothing if exposure to the sun cannot be avoided. Patients using ~~Solagé~~ Solution should practice a comprehensive sun protection program. Following discontinuation of ~~Solagé~~ Solution, patients should continue to practice a comprehensive sun protection program.

~~Solagé~~ Solution should be used with caution if you are also using other topical products with a strong drying effect on the skin, products with high concentrations of alcohol, astringents, spices or lime, medicated soaps, or shampoos, permanent wave solutions, electrolysis, hair removal products or waxes, or other preparations or processess that may dry or irritate your skin. If you are using any of these types of products, tell your doctor before using ~~Solagé~~ Solution.

What are the possible or reasonably likely side effects of ~~Solagé~~ Solution?

~~Solagé~~ Solution may cause redness, stinging, burning or irritation on areas of the skin where it is applied. It may also cause peeling and itching of the areas where applied.

Excessive or prolonged application of ~~Solagé~~ Solution may cause the treated age spots or surrounding skin to become temporarily lighter than your normally colored skin. Discontinue application of ~~Solagé~~ Solution to any such affected areas.

How can I get additional information?

This leaflet summarizes the most important information about ~~Solagé~~ Solution. If you would like more information, talk to your doctor.

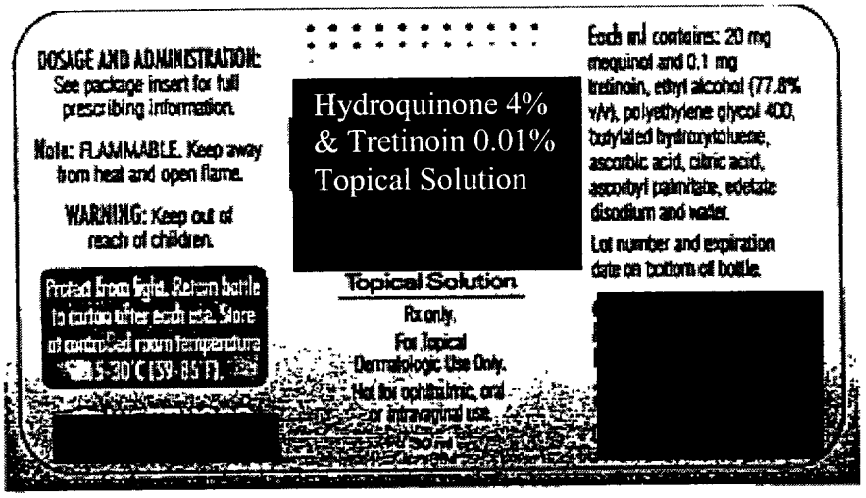
How should ~~Solagé~~ Solution be stored?

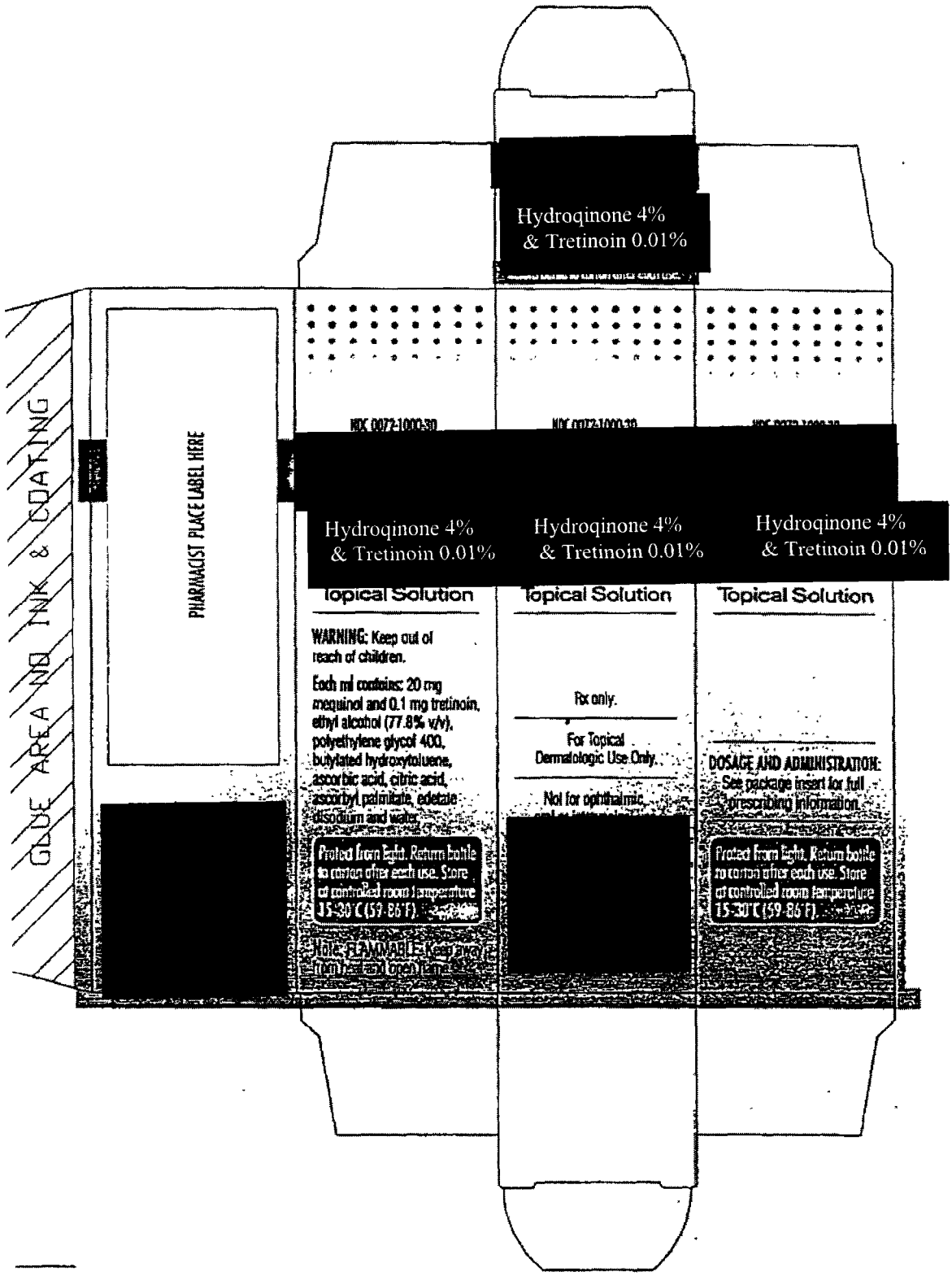
~~Solagé~~ Solution should be protected from light by returning the bottle to the carton after each use. Store at room temperature, 20° C - 25° C (68° F - 77° F).

~~Solagé~~ Solution is FLAMMABLE. Keep away from heat or open flame.

Keep this and all medication out of the reach of children.

Marketed by:


DOSAGE AND ADMINISTRATION:
See package insert for full prescribing information.
Note: FLAMMABLE. Keep away from heat and open flame.
WARNING: Keep out of reach of children.
Protect from light. Return bottle to carton after each use. Store at controlled room temperature 15-30°C (59-85°F).
Hydroquinone 4% & Tretinoin 0.01% Topical Solution
Topical Solution
Rx only.
For Topical Dermatologic Use Only.
Not for ophthalmic, oral or intravaginal use.
Each ml contains: 20 mg mequinol and 0.1 mg tretinoin, ethyl alcohol (77.8% v/v), polyethylene glycol 400, butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, edetate disodium and water.
Lot number and expiration date on bottom of bottle.


Hydroqinone 4%
& Tretinoin 0.01%
GLUE AREA NO INK & COATING
PHARMACIST PLACE LABEL HERE
Hydroqinone 4%
& Tretinoin 0.01%
Hydroqinone 4%
& Tretinoin 0.01%
Hydroqinone 4%
& Tretinoin 0.01%
Topical Solution
Topical Solution
Topical Solution
WARNING: Keep out of reach of children.
Each ml contains: 20 mg mequinol and 0.1 mg tretinoin, ethyl alcohol (77.8% v/v), polyethylene glycol 400, butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, edetate disodium and water.
Rx only.
For Topical Dermatologic Use Only.
Not for ophthalmic.
DOSAGE AND ADMINISTRATION: See package insert for full prescribing information.
Protect from light. Return bottle to carton after each use. Store at controlled room temperature 15-30°C (59-86°F).
Protect from light. Return bottle to carton after each use. Store at controlled room temperature 15-30°C (59-86°F).

Solagé™

Rx only

FPO ONLY

(mequinol 2%, tretinoin 0.01%)

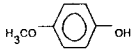
Topical Solution

For Dermatologic use only Not for ophthalmic, oral or intravaginal use

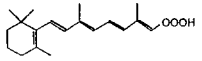
DESCRIPTION

Solagé™ Topical Solution contains mequinol 2% and tretinoin 0 01%, by weight, in a solution base of ethyl alcohol (77 8% v/v), polyethylene glycol 400, butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, edetate disodium and purified water

Mequinol is 4- hydroxyanisole, the monomethyl ether of hydroquinone or 1-hydroxy-4-methoxybenzene It has the chemical formula, $C_7H_8O_2$, a molecular weight of 124 14, and the structural formula



The chemical name for tretinoin, a retinoid, is (all *E*) 3,7 dimethyl 9-(2,6,6-trimethyl-1-cyclohexen-1 yl)-2,4,6,8-nonatetraenoic acid, also referred to as all-*trans*-retinoic acid It has the chemical formula, $C_{20}H_{28}O_2$, a molecular weight of 0 44, and the structural formula



CLINICAL PHARMACOLOGY

Solar lentigines are localized, pigmented, macular lesions of the skin on the areas of the body which have been chronically exposed to sunlight

Biopsy specimens of solar lentigines were collected in a clinical study with **Solagé** Solution at baseline, at the end of a 24 week treatment period and at the end of a subsequent 24 week, no treatment, follow-up period The end of treatment specimens showed a decrease in melanin pigmentation in both melanocytes and keratinocytes, and an increased lymphocytic infiltration, which may have been the result of irritation or an immunologic reaction The end of follow-up period specimens showed repigmentation of the melanocytes and keratinocytes to a state similar to the baseline specimens These results indicate that there is no assurance that any improvement obtained would persist upon discontinuation of drug therapy

The mechanism of action of mequinol is unknown Although mequinol is a substrate for the enzyme tyrosinase and acts as a competitive inhibitor of the formation of melanin precursors, the clinical significance of these findings is unknown The mechanism of action of tretinoin as a depigmenting agent also is unknown

PHARMACOKINETICS

The percutaneous absorption of tretinoin and the systemic exposure to tretinoin and mequinol were assessed in healthy subjects (n=8) following two weeks of twice daily topical treatment of **Solagé** Solution Approximately 0 8 mL of **Solagé** Solution was applied to a 400 cm^2 area of the back, corresponding to a dose of 37 3 $\mu g/cm^2$ for mequinol and 0 23 $\mu g/cm^2$ for tretinoin The percutaneous absorption of tretinoin was approximately 4 4%, and systemic concentrations did not increase over endogenous levels The mean C_{ss} for mequinol was 9 92 ng/mL (range 4 22 to 23 62 ng/mL) and the T_{ss} was 2 hours (range 1 to 2 hours)

INDICATIONS AND USAGE

(To understand fully the indication for this product, please read the entire **INDICATIONS AND USAGE** section of the labeling)

Solagé (mequinol 2%, tretinoin 0 01%) Topical Solution is indicated for the treatment of solar lentigines

Solagé Solution should only be used under medical supervision as an adjunct to a comprehensive skin care and sun avoidance program where the patient should primarily either avoid the sun or use protective clothing

Neither the safety nor effectiveness of **Solagé** Solution for the prevention or treatment of melasma or postinflammatory hyperpigmentation has been established

The efficacy of using **Solagé** Solution daily for greater than 24 weeks has not been established

The local cutaneous safety of using Solagé Solution in non-Caucasians has not been adequately established (see **Clinical Studies** section)

CONTRAINDICATIONS

The combination of mequinol and tretinoin may cause fetal harm when administered to a pregnant woman Due to the known effects of these active ingredients, **Solagé** Topical Solution should not be used in women of childbearing potential In a dermal teratology study in New Zealand White rabbits, there were no statistically significant differences among treatment groups in fetal malformation data, however, marked hydrocephaly with visible doming of the head was observed in one mid-dose litter (12 and 0 05 mg/kg or 132 and 0 66 mg/m^2 of mequinol and tretinoin, respectively) and two fetuses in one high dose litter (40 and 0 2 mg/kg or 440 and 2 2 mg/m^2 of mequinol and tretinoin, respectively) of **Solagé** Solution, and two high-dose tretinoin (0 2 mg/kg, 2 2 mg/m^2) treated litters These malformations were considered to be treatment related and due to the known effects of tretinoin This was further supported by coincident appearance of other malformations associated with tretinoin, such as cleft palate and appendicular skeletal defects No effects attributed to treatment were observed in rabbits in that study treated topically with mequinol alone (dose 40 mg/kg, 440 mg/m^2) A no-observed-effect level (NOEL) for teratogenicity in rabbits was established at 4 and 0 02 mg/kg (44 and 0 22 mg/m^2 mequinol and tretinoin, respectively) for **Solagé** Solution which is approximately the maximum possible human daily dose, based on clinical application to 5% of total body surface area Plasma tretinoin concentrations were not raised above endogenous levels, even at teratogenic doses Plasma mequinol concentrations in rabbits at the NOEL at one hour after application were 124 ng/mL or approximately twelve times the mean peak plasma concentrations of that substance seen in human subjects in a clinical pharmacokinetic study

In a repeated study in pregnant rabbits administered the same dose levels as the study described above, additional precautionary measures were taken to prevent ingestion, although there is no evidence to confirm that ingestion occurred in the initial study Precautionary measures additionally limited transdermal absorption to a six hour exposure period, or approximately one fourth of the human clinical daily continuous exposure time This study did not show any significant teratogenic effects at doses up to approximately 13 times the human dose on a mg/m^2 basis However, a concurrent tretinoin dose group (0 2 mg/kg/day) did include two litters with limb malformations

In a published study in albino rats (J Am Coll Toxicology 4(5) 31-63, 1985), topical application of 5% of mequinol in a cream vehicle during gestation was embryotoxic and embryolethal Embryonic loss prior to implantation was noted in that study where animals were treated throughout gestation Coincidentally, mean preimplantation embryonic loss was increased in the first rabbit study in all mequinol treated groups, relative to control, and in the high dose mequinol/tretinoin and tretinoin only treated groups in the second study In those studies, dosing began at gestation day 6, when implantation is purported to occur Increased preimplantation loss was also noted at the high combination dose in a study of early embryonic effects in rats, as was decreased body weight in male pups, these findings are consistent with the published study

Solagé Solution was not teratogenic in Sprague-Dawley rats when given in topical doses of 80 and 0 4 mg/kg mequinol and tretinoin, respectively (480 and 2 4 mg/m^2 or 11 times the maximum human daily dose) The maximum human dose is defined as the amount of solution applied daily to 5% of the total body surface area

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone Thirty cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin Although no definite pattern of teratogenicity and no causal association has been established from these cases, 6 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain) The significance of these spontaneous reports in terms of risk to the fetus is not known

No adequate or well-controlled trials have been conducted with **Solagé** Solution in pregnant women

Solagé Topical Solution is contraindicated in individuals with a history of sensitivity reactions to any of its ingredients It should be discontinued if hypersensitivity to any of its ingredients is noted

WARNINGS

Solagé Solution is a dermal irritant and the results of continued irritation of the skin for greater than 52 weeks in chronic, long-term use are not known Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with utmost caution in patients with this condition

Safety and effectiveness of **Solagé** Solution in individuals with moderately or heavily pigmented skin have not been established

Solagé Solution should not be administered if the patient is also taking drugs known to be photosensitizers (e g , thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) to treated areas should be avoided or minimized during the use of **Solagé** Solution Patients must be advised to use protective clothing and comply with a comprehensive sun avoidance program when using **Solagé** Solution Data are not available to establish how or whether **Solagé** Solution is degraded (either by sunlight or by normal interior lighting) following application to the skin Patients with sunburn should be advised not to use **Solagé** Solution until fully recovered Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using **Solagé** Solution and ensure that the precautions outlined in the Patient Medication Guide are observed

Solagé Solution should be kept out of the eyes, mouth, paranasal creases, and mucous membranes **Solagé** Solution may cause skin irritation, erythema, burning, stinging or tingling, peeling, and pruritis If the degree of such local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether The efficacy at reduced frequencies of application has not been established

Solagé Solution should be used with caution by patients with a history, or family history, of vitiligo One patient in the trials, whose brother had vitiligo, experienced hypopigmentation in areas that had not been treated with study medication Some of these areas continued to worsen for at least one month post treatment with **Solagé** Solution Six weeks later the severity of the hypopigmentation had decreased from moderate to mild and 106 days post treatment, the patient had resolution of some but not all lesions

Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, discomfort, or hypopigmentation of the skin may occur

PRECAUTIONS

General

For external use only

Solagé Solution should only be used as an adjunct to a comprehensive skin care and sun avoidance program (See **INDICATIONS AND USAGE** section)

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of **Solagé** Solution should be discontinued

Weather extremes, such as wind or cold, may be more irritating to patients using **Solagé** Solution

Information for patients

Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety The Patient Medication Guide is attached to this Package Insert

Drug Interactions

Concomitant topical products with a strong skin drying effect, products with high concentrations of alcohol, astringents, spices or lime, medicated soaps or shampoos, permanent wave solutions, electrolysis, hair depilatories or waxes, or other preparations that might dry or irritate the skin should be used with caution in patients being treated with **Solagé** Solution because they may increase irritation when used with **Solagé** Solution

Solagé Solution should not be administered if the patient is also taking drugs known to be photosensitizers (e g , thiazides, tetracyclines, fluoroquinolones, phenothiazines sulfonamides) because of the possibility of augmented phototoxicity

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although a dermal carcinogenicity study in CD 1 mice indicated that **Solagé** Solution applied topically at daily doses up to 80 and 0 4 mg/kg (240 and 1 2 mg/m^2) of mequinol and tretinoin, respectively, representing approximately 5 times the maximum possible systemic human exposure was not carcinogenic, in a photocarcinogenicity study utilizing Crl Skh 1(hr/hr BR) hairless albino mice, median time to onset of tumors decreased Also, the number of tumors increased in all dose groups administered 1 4, 4 3 or 14 µl of **Solagé** Solution/cm^2 of skin (24 and 0 12, 72 and 0 36, or 240 and 1 2 mg/m^2 of mequinol and tretinoin, respectively, 0 5, 1 9, or 6 5 times the daily human dose on a mg/m^2 basis) following chronic topical dosing with intercurrent exposure to ultraviolet radiation for up to 40 weeks Similar animal studies have shown an increased tumorigenic risk with the use of retinoids when followed by ultraviolet radiation Although the significance of these studies to human use is not clear, patients using this product should be advised to avoid or minimize exposure to either sunlight or artificial ultraviolet irradiation sources

Solagé™ Topical Solution Medication Guide

(mequinol 2%, tretinoin 0.01%)

INFORMATION FOR PATIENTS

Please read this Medication Guide carefully before you start to use your medicine. If you have any questions, or are not sure about any of the information on Solagé Solution, ask your doctor.

The active ingredients in **Solagé** Solution (pronounced so-la-JAY) are mequinol and tretinoin

Solagé Solution also contains ethlyl alcohol (77 8% v/v), polyethylene glycol 400, butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, edetate disodium, and purified water

What is the Most Important Information about Solagé Solution?

Solagé Solution is a prescription medication It should only be used under supervision of your doctor as part of a sun avoidance program This program should also include avoiding exposure to artificial sunlight (sunlamps) and avoidance of direct sunlight by wearing protective clothing

Solagé Solution does not permanently "cure" solar lentigines, also known as brown "age" or "liver" spots In clinical trials, most patients experienced some degree of darkening of their spots over time

Follow the instructions for application of **Solagé** Solution carefully Avoid getting the medication on your normal-toned skin, in your eyes, nose, or mouth

Solagé Solution can cause the side effect, halo hypopigmentation, which is lightening of the skin surrounding the spot being treated, within the 6 month treatment period.

Warning: Solagé Solution should not be used if you are pregnant, attempting to become pregnant, or at a high risk of pregnancy. Consult your doctor for adequate birth control measures if you are a female of child-bearing potential. Avoid sunlight and any other medicines that may increase your sensitivity to sunlight (see below).

There is very limited information on the safety of **Solagé** Solution in people with moderately or darkly pigmented skin

What Can I Expect From Solagé Solution?

Solagé Solution is a prescription medication used for the topical treatment of solar lentigines, also known as brown "age" or "liver" spots

Studies show that after 24 weeks, for lesions of the face, 57% of patients using **Solagé** Solution had moderate improvement or greater, with 3% experiencing complete clearing of all treated lesions Another 28% of patients had slight improvement and 15% had no change or worse (less than 1% of patients had worsening of their lesions) After 24 weeks for lesions of the forearms/back of hands, 54% of patients using **Solagé** Solution experienced moderate improvement or greater, with 1% experiencing complete clearing of all treated lesions Another 26% had slight improvement and 20% had no change or worse (less than 1% of patients had worsening of their lesions)

Approximately 9% of patients who had success in the treatment of their age spots also experienced the side effect, halo hypopigmentation, which is lightening of skin surrounding the treated spot Evidence has not been established concerning the effectiveness of **Solagé** Solution in the treatment of other hyperpigmented conditions of the skin

Improvement in the color of the treated age spots occurs gradually. Don't be discouraged if you see no immediate improvement Be patient If **Solagé** Solution is going to have a beneficial effect for you, it may take up to six months of treatment before full beneficial effects are seen After stopping treatment with **Solagé** Solution, the age spots may darken again over time

The effectiveness of **Solagé** Solution in treating solar lentigines, also known as brown "age" or "liver" spots, beyond 6 months has not been established

Who should not use Solagé Solution?

Solagé Solution should not be used if you are pregnant, attempting to become pregnant, or at a high risk of pregnancy Consult your doctor for adequate birth control measures if you are a female of child-bearing potential

It is not known if **Solagé** Solution is passed to infants through breast milk Do not use **Solagé** Solution if you intend to breast feed, unless advised otherwise by your doctor

Solagé Solutuion should not be used on children

Do not use **Solagé** Solution if you are allergic to any ingredients in this medicine If you are allergic to any of the ingredients, tell your doctor

If you are sunburned, do not use **Solagé** Solution until you have fully recovered

Do not use **Solagé** Solution if you have a skin condition called eczema or other inflamed or irritated chronic skin conditions

Do not use **Solagé** Solution if you are inherently sensitive to sunlight or taking other drugs that increase your sensitivity to sunlight You should tell your physician if you are also using other medicines that increase sensitivity to sunlight These medications include but are not limited to thiazides (used to treat high blood pressure), tetracyclines, fluoroquinolones or sulfonamides (used to treat infection), and phenothiazines (used to treat serious emotional problems) If you are taking any prescription medicines, non-prescription medicines or using any facial or skin creams, check with

your physician to make sure they do not interact with **Solagé** Solution

There is very limited information on the safety of **Solagé** Solution in people with moderately or darkly pigmented skin If you, or a family member, have a history of vitiligo (a skin condition consisting of white patches on various parts of the body), consult your doctor before using **Solagé** Solution

How should I use Solagé Solution?

Solagé Solution is to be used twice daily, at least eight hours apart, or as directed by your doctor It is a drug for topical use only and is not a cosmetic preparation Do not use **Solagé** Solution around your eyes, lips, creases of the nose or mucous membranes **Solagé** Solution may cause severe redness, itching, burning, stinging, and peeling if applied to these areas If the product gets in your eyes, rinse thoroughly with water and contact your doctor

Apply **Solagé** Solution to the age spots using the applicator provided with the medication Avoid application of **Solagé** Solution to the surrounding, normally colored skin Only enough **Solagé** Solution should be applied to make the lesion appear moist – running or dripping of the medication should be avoided Applications of larger amounts of **Solagé** Solution, or more frequent applications than recommended, will not lead to more rapid or better results, and marked redness, peeling, irritation or hypopigmentation may occur You should not shower or bathe the treatment areas for at least 6 hours after application of **Solagé** Solution

Stop treating any age spots that become the same color or lighter than your normally colored skin If the skin surrounding an age spot becomes lighter than your normally colored skin, stop treating that age spot and contact your doctor regarding continued use of **Solagé** Solution to that age spot.

If you forget or miss a dose of **Solagé** Solution, do not try to "make it up " Return to your normal application schedule as soon as you can

If sensitivity or increased irritation occurs, stop use of **Solagé** Solution and contact your doctor

If the age spots become darker with treatment, stop use of **Solagé** Solution and contact your doctor

Do not use **Solagé** Solution for any condition other than for which it was prescribed by your doctor Do not give it to other persons or allow other persons to use it

You may use cosmetics after applying **Solagé** Solution but you should wait 30 minutes before applying

What should I avoid while using Solagé Solution?

Solagé Solution increases your sensitivity to sunlight Sun exposure (natural or artificial) to areas of the skin treated with **Solagé** Solution should be avoided Wear protective clothing if exposure to the sun cannot be avoided Patients using **Solagé** Solution should practice a comprehensive sun protection program Following discontinuation of **Solagé** Solution, patients should continue to practice a comprehensive sun protection program

Solagé Solution should be used with caution if you are also using other topical products with a strong drying effect on the skin, products with high concentrations of alcohol, astringents, spices or lime, medicated soaps, or shampoos, permanent wave solutions, electrolysis, hair removal products or waxes, or other preparations or processess that may dry or irritate your skin If you are using any of these types of products, tell your doctor before using **Solagé** Solution

What are the possible or reasonably likely side effects of Solagé Solution?

Solagé Solution may cause redness, stinging, burning or irritation on areas of the skin where it is applied It may also cause peeling and itching of the areas where applied

Excessive or prolonged application of **Solagé** Solution may cause the treated age spots or surrounding skin to become temporarily lighter than your normally colored skin Discontinue application of **Solagé** Solution to any such affected areas

How can I get additional information?

This leaflet summarizes the most important information about **Solagé** Solution. If you would like more information, talk to your doctor

How should Solagé Solution be stored?

Solagé Solution should be protected from light by returning the bottle to the carton after each use Store at room temperature, 20° C - 25° C (68° F - 77° F)

Solagé Solution is FLAMMABLE. Keep away from heat or open flame

Keep this and all medication out of the reach of children.

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Fort Worth, Texas 76177 USA
Manufactured by
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Buffalo, NY 14213 USA
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Mequinol was non-mutagenic in the Ames/Salmonella assay using strains TA98, TA100, TA1535, and TA1537, all of which are insensitive to mutagenic effects of structurally related quinones **Solagé** Solution was non-genotoxic in an *in vivo* dermal micronucleus assay in rats, but exposure of bone marrow to drug was not demonstrated

A dermal reproduction study with **Solagé** Solution in Sprague-Dawley rats at a daily dose of 80 and 0 4 mg/kg (480 and 2 4 mg/m²) of mequinol and tretinoin, respectively, approximately 11 times the corresponding maximum possible human exposure, assuming 100% bioavailability following topical application to 5% of the total body surface area, showed no impairment of fertility

Pregnancy Teratogenic effects Pregnancy Category X

Although the magnitude of the potential for teratogenicity may not be well-defined, **Solagé** Solution is labeled as an "X" because the potential risk of the use of this drug to treat this particular indication (solar lentigines) in a pregnant woman clearly outweighs any possible benefit (see **CONTRAINDICATIONS** section)

Nursing Mothers It is not known to what extent mequinol and/or tretinoin is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when **Solagé** Solution is administered to a nursing woman

Pediatric Use The safety and effectiveness of this product have not been established in pediatric patients **Solagé** Solution should not be used on children

Geriatric Use Of the total number of patients in clinical studies of **Solagé** Solution, approximately 43% were 65 and older, while approximately 8% were 75 and over No overall differences in effectiveness or safety were observed between these patients and younger patients

ADVERSE REACTIONS

In clinical trials, adverse reactions were primarily mild to moderate in intensity, occurring in 66% and 30% of patients, respectively The majority of these events were limited to the skin and 64% had an onset of a skin related adverse reaction early in treatment (by week 8) The most frequent adverse reactions in patients treated with **Solagé** Solution were erythema (49% of patients), burning, stinging, or tingling (26%), desquamation (14%), pruritus (12%), and skin irritation (5%)

Some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%) Ninety-four of 106 patients (89%) had resolution of hypopigmentation upon discontinuation of treatment to the lesion, and/or re-instruction on proper application to the lesion only Another 8% (9/106) of patients with hypopigmentation events had resolution within 120 days after the end of treatment Three of the 106 patients (2 8%) had persistence of hypopigmentation beyond 120 days Approximately 6% of patients discontinued study participation with **Solagé** Solution due to adverse reactions These discontinuations were due primarily to skin redness (erythema) or related cutaneous adverse reactions **Solagé** Solution was generally well tolerated

Adverse Events Occurring in >1% of the Population —All Studies

Body System	Solagé Solution (mequinol 2%, tretinoin 0 01%)		Tretinoin, 0 01%		Mequinol, 2%		Vehicle	
	N	%	N	%	N	%	N	%
Skin and Appendages Erythema	549	44.6	261	55.3	13	5 1	8	4 6
Burning/Stinging/ Tingling	270	21 9	173	36 7	26	10 2	20	11 4
Desquamation	155	12 6	93	19 7	7	2 8	2	1 1
Pruritus	135	11 0	66	14 0	12	4 7	3	1.7
Irritation Skin	90	7 3	25	5 3	1	0 4	1	0 6
Halo Hypopigmentation	76	6 2	16	3 4	2	0 8	2	1 1
Hypopigmentation	50	4 1	8	1 7	2	0 8	0	0 0
Skin Dry	38	3 1	18	3 8	3	1 2	1	0 6
Rash	31	2 5	21	4 4	0	0 0	1	0 6
Crusting	30	2 4	18	3 8	0	0 0	1	0 6
Rash Vesicular Bullae	18	2.1	8	1.7	0	0 0	0	0 0
Dermatitis	25	2 0	0	0 0	0	0 0	0	0 0

OVERDOSAGE

If **Solagé** Solution is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, discomfort, or hypopigmentation may occur Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of vitamin A (hypervitaminosis A) If oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary The maximal no effect level for oral administration of **Solagé** Solution in rats was 5 0 mL/kg (30 mg/m²) Clinical signs observed were attributed to the high alcohol content (77%) of the drug formulation

DOSAGE AND ADMINISTRATION

Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety The physician should review the Patient Medication Guide

Apply **Solagé** Solution to the solar lentigines using the applicator tip while avoiding application to the surrounding skin Use twice daily, morning and evening at least 8 hours apart, or as directed by a physician Patients should not shower or bathe the treatment areas for at least 6 hours after application of **Solagé** Solution Special caution should be taken when applying **Solagé** Solution to avoid the eyes, mouth, paranasal creases, and mucous membranes

Application of **Solagé** Solution may cause transitory stinging, burning or irritation

Improvement continues gradually through the course of therapy and should be apparent by 24 weeks Patients should avoid exposure to sunlight (including sunlamps) or wear protective clothing while using **Solagé** Solution Data are not available to establish how or whether **Solagé** Solution is degraded (either by sunlight or by normal interior lighting) following application to the skin

With discontinuation of **Solagé** Solution therapy, a majority of patients will experience some repigmentation over time of their lesions

Applications of larger amounts of medication or more frequently than recommended will not lead to more rapid or better results, and marked redness, peeling, irritation, or hypopigmentation (abnormal lightening) of the skin may occur

Patients treated with **Solagé** Solution may use cosmetics but should wait 30 minutes before applying

Clinical Studies

Two adequate and well-controlled trials evaluated changes in treated hyperpigmented lesions on the face, forearms/back of hands in 421 patients treated with **Solagé** Topical Solution, 422 patients treated with tretinoin topical solution, 209 patients treated with mequinol topical solution and 107 patients treated with vehicle for up to 24 weeks In these studies, patients were to avoid sun exposure and use protective clothing, and use of sunscreens was prohibited Patients were allowed to apply Moisturel® Lotion 30 minutes after application of **Solagé** Solution Physicians assessed the extent of improvement or worsening of all the treated lesions from the baseline condition on a 7 point scale The results of these evaluations are shown below

	Face		Forearms/Back of Hands	
	Solagé Solution	Vehicle	Solagé Solution	Vehicle
Moderate Improvement or greater[1]	57%	15%	54%	14%
Slight Improvement	28%	36%	26%	33%
No Change[2]	15%	49%	20%	53%

[1] Includes the following grades Moderate Improvement, Marked Improvement, Almost Clear, Completely Clear Moderate Improvement or greater was considered clinically meaningful

[2] Includes the following grades No Change, Worse (less than 1% of patients treated with **Solagé** Solution were rated as worse)

Improvement (lightening) of the solar lentigines occurred gradually over time during the 24 week treatment period At 24 weeks of treatment, 57% and 54% of patients experienced moderate improvement or greater, and 3% and 1% of patients were completely clear of all treated lesions for the face and forearms/back of hands, respectively It should be noted that approximately 9% of patients, from both treatment areas in these studies, with moderate improvement or greater also experienced hypopigmentation of the skin surrounding at least one treated lesion There are no vehicle controlled effectiveness data on the course of lesions treated beyond 24 weeks

After 24 weeks of treatment, for the forearm/back of hands treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 38%, 37%, and 26%, respectively, and for mequinol topical solution were 24%, 40%, and 36%, respectively For the face treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 46%, 33%, and 21%, repectively, and for mequinol topical solution were 33%, 30%, and 37% respectively

The duration of effect was investigated during a period of up to 24 weeks following the discontinuation of treatment Results from these studies showed that patients may maintain the level of clinical improvement of their treated lesions from the end of treatment through the 24 week follow up period However, some degree of repigmentation of treated lesions was observed over time, demonstrating reversibility of the depigmenting action of **Solagé** Solution

In the clinical studies, some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%) Hypopigmentation of the skin surrounding treated lesions occurs even in the setting of proper application of the drug within the lesion border The majority (94/106 - 89%) resolved upon discontinuation of treatment to the lesion, and/or re-instruction on proper application to the lesion only Another 8% (9/106) of patients with hypopigmentation events had resolution within 120 days after the end of treatment

Three of the 106 patients (2 8%) had persistence of hypopigmentation beyond 120 days This further demonstrates the reversibility of the depigmenting action of **Solagé** Solution

Over 150 patients used **Solagé** Solution twice daily for 52 weeks in an open label clinical study The safety profile for **Solagé** Solution in this long term study was similar to that seen in the 24 week studies although burning/stinging/ tingling, desquamation, pruritis, and irritation of the skin occurred at lower rates and halo hypopigmentation and hypopigmentation occurred at a slightly greater rate

Over 90 patients used **Solagé** Solution twice daily and a concomitant sunscreen (PreSun® 29) daily for up to 24 weeks in an open label clinical study The safety profile for **Solagé** Solution in this study was similar to that seen in studies which prohibited sunscreen use although desquamation, pruritis, and halo hypopigmentation occurred at slightly lower rates

The clinical studies of **Solagé** Solution included 1794 individuals of Skin Type I-V, 94 5% of whom were Caucasian The trials also included 5% of individuals who were Asian/Pacific Islander– 1 2%, African-American–0 8%, and Hispanic/Latino–3 5% Safety in Asian/Pacific Islander, African-American, and Hispanic/Latino individuals has not been adequately established Safety and effectiveness of **Solagé** Solution in individuals with Skin Type VI (never burns from the sun, deeply pigmented skin) or women of childbearing potential have not been established (see CONTRAINDICATIONS)

HOW SUPPLIED. Solagé (mequinol 2%, tretinoin 0 01%) Topical Solution is available in 30 mL plastic bottles with an applicator **NDC** 0299-5970-30

STORAGE The bottle should be protected from light by continuing to store in the carton after opening Store at controlled room temperature, 20° - 25° C (68° 77° F)

Note: FLAMMABLE Keep away from heat and open flame

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